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Daniel Carlat, MD
Editor-in-Chief

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IN THIS ISSUE

Focus of the Month: **Neurobiology**

Learning Objectives

After reading these articles, you should be able to:

1. Analyze the results of the most recent meta-analysis on antidepressant efficacy to inform pharmacological decisions.
2. Describe the significance of understanding the neuroscience behind common disorders as well as their corresponding pharmacological treatments.
3. Summarize some of the current findings in the literature regarding psychiatric treatment.

A Look at the Latest Antidepressant Meta-Analysis

Adam Strassberg, MD. Psychiatrist in private practice in Palo Alto, CA. Contributing writer to the Carlat newsletters.

Dr. Strassberg has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

In Summary

- This meta-analysis represents the most-comprehensive evidence to date on the efficacy of antidepressants.
- Among antidepressants available in the U.S., those with the best combination of response and tolerability were escitalopram, mirtazapine, paroxetine, and sertraline.

You may have read about the meta-analysis published in *Lancet* earlier this year on the efficacy evidence for all antidepressants (Cipriani A et al, *Lancet* 2018;391(10128):1357–1366). It's a complicated paper, and in this article, we'll take a closer look at it and give you our take on the bottom line.

The authors did a systematic review and meta-analysis, searching published and unpublished, double-blind, randomized controlled trials up to January 2016, notably also including the largest amount of unpublished data to date.

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Q&A With the Expert

Neurobiology Concepts for Psychiatrists

David M. Kaufman, MD

Department of Neurology, Montefiore Medical Center, Bronx, NY. Co-author of Kaufman's Clinical Neurology for Psychiatrists, *8th ed. (Elsevier).*

Dr. Kaufman has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

TCPR: I think that a lot of psychiatrists, myself included, could use a refresher course on Parkinson disease and how to distinguish its symptoms from those induced by antipsychotics (parkinsonism). What exactly is parkinsonism?

Dr. Kaufman: Parkinsonism is a clinical syndrome comprised primarily of rigidity, tremor, and bradykinesia (slowed movements). The most common cause of parkinsonism is Parkinson disease, but parkinsonism also can occur from the use of any medication that blocks the D2 (dopamine type 2) receptor. Those include antipsychotics but can also include non-psychiatric medicines, particularly metoclopramide (Reglan), an anti-nausea medicine. So, we see parkinsonism in people who are being treated for nausea and vomiting associated with prolonged migraines, chemotherapy, and pregnancies. In addition, vesicular monoamine transporter 2 (VMAT2) inhibitors such as deutetrabenazine (Austedo), tetrabenazine (Xenazine), and valbenazine (Ingrezza)—medications that reduce tardive dyskinesia, chorea in Huntington disease, or both—have recently been reported to induce parkinsonism as an adverse effect.

TCPR: What other disorders might cause parkinsonism?

Dr. Kaufman: In addition to parkinsonism being related to antipsychotics and other medications, psychiatrists need to consider the

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A Look at the Latest Antidepressant Meta-Analysis

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Both placebo-controlled and head-to-head trials were included across 21 antidepressants, and each evaluated monotherapy for the acute treatment of adults with unipolar major depression. In total, the authors analyzed 522 trials covering 116,477 participants.

The primary outcomes were "efficacy" and "acceptability." Efficacy was defined as the response rate at 8 weeks as measured by a reduction of ≥ 50% of the total score on a standardized depression rating scale. Acceptability was defined as treatment discontinuation as measured by the proportion of patients who withdrew from a study for any reason by 8 weeks.

Here are some of the more interesting findings:

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Head-to-Head Antidepressants Analyzed in Antidepressant Study

More Effective	Less Effective	More Acceptable	Less Acceptable
*Agomelatine	Fluoxetine	*Agomelatine	Amitriptyline
Amitriptyline	Fluvoxamine	Citalopram	Clomipramine
Escitalopram	*Reboxetine	Escitalopram	Duloxetine
Mirtazapine	Trazodone	Fluoxetine	Fluvoxamine
Paroxetine		Sertraline	*Reboxetine
Venlafaxine		Vortioxetine	Trazodone
Vortioxetine			Venlafaxine

**Not approved for use in the U.S.*

- All antidepressants were more effective than placebo, with odds ratios (OR) ranging from 2.13 for amitriptyline to 1.37 for reboxetine (a norepinephrine reuptake inhibitor not approved in the US). For acceptability, only agomelatine (an atypical agent not approved in the US, OR 0.84) and fluoxetine (OR 0.88) were associated with fewer dropouts than placebo, while clomipramine was associated with more dropouts than placebo (OR 1.30).
- In head-to-head trials, certain antidepressants were more efficacious than others, and several had more acceptability in terms of dropout rates due to side effects. Agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine were more effective than other antidepressants (ORs 1.19–1.96), while fluoxetine, fluvoxamine, reboxetine, and trazodone were least efficacious (ORs 0.51–0.84). For tolerability, agomelatine, citalopram, escitalopram, fluoxetine, sertraline, and vortioxetine were more acceptable than other agents (ORs 0.43–0.77), while dropout rates were highest for amitriptyline, clomipramine, duloxetine, fluvoxamine, reboxetine, trazodone, and venlafaxine (ORs 1.30–2.32).
- The authors don't directly recommend any drugs over others—they mostly present significant amounts of data. However, in their discussion, they note "some antidepressants, such as escitalopram, mirtazapine, paroxetine, agomelatine, and sertraline had a relatively higher response and lower dropout rates than other antidepressants. By contrast, reboxetine, trazodone, and fluvoxamine were associated with generally inferior efficacy and acceptability profiles compared with other antidepressants."
- Industry funding was not associated with substantial differences in outcomes for either response or dropout rates.

How might this study change the way you choose antidepressants? To better understand the analysis, *TCPR* interviewed John Ioannidis, MD, one of the study's authors, and Professor of Medicine, Health Research and Policy, and Biomedical Data Science at the Stanford University School of Medicine. Dr. Ioannidis offered the following insight:

- The results overall suggest that antidepressants on average have modest/small efficacy.
- Looking at individual antidepressants, mirtazapine ranks close to the top for efficacy and is about average for acceptability; amitriptyline ranks at the top in efficacy and is ranked a bit better than average for acceptability; venlafaxine ranks high on efficacy but low on acceptability; and paroxetine ranks modestly, roughly average in both. You can use these rankings to inform your decisions about which antidepressants to choose (see table above).
- The differences between antidepressants were very modest, even smaller than the differences between antidepressants and placebo. These differences may represent chance or bias.
- The meta-analysis does not support the idea that antidepressants are entirely useless. On average, they do have small/modest benefit. At the same time, the meta-analysis focused on short-term treatment of patients with well-documented major depression, typically moderate or severe major depression. Also, this meta-analysis provides no evidence—positive or negative—regarding the long-term use of antidepressants.

TCPR VERDICT: No big surprises in this study, which shows that SSRIs have the best combination of efficacy and tolerability—though efficacy is modest.

Expert Interview—Neurobiology Concepts for Psychiatrists

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possibility that parkinsonism can be a manifestation of neurologic illnesses, including Lewy body dementia, Wilson disease, drug abuse, or Huntington disease, at least its juvenile form. These particular illnesses are especially important because they cause mood and thought disorders, as well as parkinsonism, and thus a patient developing one of them may see a psychiatrist before any other specialist.

TCPR: Can you tell us more about how we determine diagnostically whether parkinsonism is due to the use of antipsychotics or Parkinson disease? Could it be both?

Dr. Kaufman: It could be both, especially in older adults. If older patients have been receiving antipsychotics and develop parkinsonism, a psychiatrist might consider that these patients may have been developing idiopathic Parkinson disease and that the psychiatric symptoms may have been related. It is not always easy to tell the difference between the disease and its adverse effects. The first thing to do, if possible, is to stop the antipsychotic agent and wait 3 weeks to 3 months to see if the symptoms resolve. If the psychiatrist cannot discontinue the antipsychotic, the next strategies would be to reduce the dose, switch to a second-generation antipsychotic, or use clozapine. In equivocal cases, or when there is urgency, there is a new nuclear medicine test called a dopamine transporter scan (DaT) that usually can reliably distinguish between Parkinson disease and medication-induced parkinsonism (Bhattacharjee S, Ng KL, *Indian J Nucl Med* 2016;31(4):320–321).

TCPR: How should we examine a patient who appears to have parkinsonism?

Dr. Kaufman: To start, observe whether the patient has reduced facial and limb expressions and gestures. For example, there may be decreased smiling and decreased affect. The patient will not make any hand gestures. There will also be characteristically fewer eye blinks and a tendency to stare, which neurologists call a "reptilian stare." In most cases, a patient with parkinsonism will have a tremor of one or both hands. If it is unilateral or asymmetric, a resting tremor suggests idiopathic Parkinson disease, but if it is symmetric, we really cannot say whether it is idiopathic or medication-induced.

TCPR: After we make those observations, what should we do next?

Dr. Kaufman: Neurologists rotate the hand around the wrist and see if there is cogwheel resistance. Both wrists need to be tested. In individuals who have a tremor on one side, that wrist ought to have rigidity, and the other one will not. Another maneuver is the so-called "pull test." With the patient standing, the physician stands behind the patient, hands on the patient's shoulders, and says, "At the count of 3, I'm going to pull you back a little." During this, a normal healthy patient will take a step back or bend the shoulders backwards to maintain balance. In contrast, someone with Parkinson disease will either take many steps backwards ("retropulsion") or just topple over like a statue ("falling *en bloc*"). Another simple thing we do is watch people walk to see if they have normal arm swing. A lack of normal swinging on one or both sides is consistent with parkinsonism.

"When people come to grips with the fact that they have developed a neurodegenerative disorder (idiopathic Parkinson disease), they have to deal with the usual psychological problems of loss. These are losses that could be ameliorated by psychotherapy, vocational counseling, and physical therapy. With a regimen of Parkinson medications, people usually maintain all their normal activities for five years."

David M. Kaufman, MD

TCPR: Interesting. How do you suggest we evaluate tremors in these patients? And can you clarify the difference between intention tremors and resting tremors?

Dr. Kaufman: Parkinson disease is usually associated with a resting tremor. That is, a tremor of 4–6 Hertz (Hz, cycles per second) in one or both hands, in which the fingers and the hand repeatedly flex. Although this tremor is present at rest, patients actually can suppress it for several seconds to several minutes. We ask patients, "Please stop the shaking as I count to 10." Patients will also have a diminished tremor when we ask them, "Take your finger and move it from your nose to my finger, then go back and forth." And, when a patient is holding the hands in fixed positions against gravity—say, straight out—the tremor will be reduced compared to when the patient holds the hands at rest.

TCPR: So, in parkinsonism we would see a resting tremor. When would we see an intention tremor?

Dr. Kaufman: A common intention tremor is "essential tremor," which is more frequent, develops in younger individuals, and frequently has developed in a patient's family members. This tremor is a more rapid tremor and is not present when patients have their hands in their lap, but is present when the arms are held in fixed positions against gravity—for example, when the patient sticks out both hands for 10 seconds.

TCPR: Are there any clues during the exam that might make you think that what you are seeing is more likely drug-induced parkinsonism?

Dr. Kaufman: Well, if it's asymmetric or unilateral, it is more likely to be idiopathic Parkinson disease. But otherwise—putting aside the history, of course—it is hard to tell the two apart.

TCPR: Moving on to idiopathic Parkinson disease, let's talk about the complications or psychiatric conditions that could develop in patients. What is the timing of some of these psychiatric symptoms?

Dr. Kaufman: Initially, when people come to grips with the fact that they have developed a neurodegenerative disorder, they have to deal with the usual psychological problems of loss. People often must retire, curtail their social life, and cut back on their

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Expert Interview–Neurobiology Concepts for Psychiatrists

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physical activities. These are losses that could be ameliorated by psychotherapy, vocational counseling, and physical therapy. With a regimen of Parkinson medications, such as carbidopa/levodopa and/or dopamine agonists, people usually maintain all their normal activities for five years.

TCPR: Switching to treatment for drug-induced parkinsonism, what's your take on using anticholinergics?

Dr. Kaufman: The idea is that there is an imbalance in Parkinson disease between dopamine activity and cholinergic activity, and if you give an anticholinergic and reduce the cholinergic activity, you will counterbalance the deficit in dopamine activity. Although anticholinergics may reduce the tremor of Parkinson disease, their potential side effects are daunting. After all, we are dealing generally with an older population, and the doses that we need to suppress the tremor cause cognitive impairment and delirium.

TCPR: What are your thoughts on the dilemma of treating psychosis and Parkinson disease, where dopamine is already depleted and you're prescribing dopamine blockers?

Dr. Kaufman: The psychosis in Parkinson disease tends to be worse at bedtime. Its hallmarks are paranoia and visual hallucinations. Of course, unnecessary medications, whether or not they cause psychosis, should be discontinued. Then, less potent Parkinson disease medications should be tapered if not discontinued. Typically, our go-to antipsychotics were—and still are, for many clinicians—the lower-potency antipsychotics, such as quetiapine and clozapine. Quetiapine's effectiveness in this situation is still not established. Clozapine is effective for psychosis in Parkinson patients, but it is difficult to prescribe because of the white blood count monitoring requirement (see *TCPR*, "Clozapine: A Fresh Look," March 2018). One medication that may reduce hallucinations in Parkinson disease patients is pimavanserin (Nuplazid). However, because recent reports have described excess mortality in Parkinson disease patients taking this medicine, it now carries a "black box warning." Moreover, I haven't seen any data comparing pimavanserin to quetiapine or clozapine.

TCPR: Moving on, I'd like to touch on another hot topic in neuropsychiatry—frontotemporal dementia vs Alzheimer dementia. How common is frontotemporal dementia, and how is it different clinically from Alzheimer dementia?

Dr. Kaufman: Frontotemporal dementia (FTD) is much more common in younger populations—meaning under the age of 65. Among this age group, FTD is about as prevalent as Alzheimer dementia (AD). However, among those older than 65, AD is much more common. Incidentally, what we call AD is often actually a combination of vascular dementia and AD.

TCPR: So, how would we know if somebody had frontotemporal dementia?

Dr. Kaufman: Patients with frontotemporal dementia typically present with changes in or loss of executive function, inhibition, or language function that are at least as prominent as cognitive impairment. They will often, on one hand, be uninhibited in their speech and their activities, but they may have marked apathy, reticence, and in some cases primary aphasia—a loss of language ability. In contrast, people with Alzheimer disease generally present with loss of memory and then loss of judgment. In neither case are there clear physical deficits. Neither group of patients will have paralysis or gait impairment; however, because of the frontal lobe degeneration, frontotemporal dementia patients often have pseudobulbar palsy. As far as confirmatory tests, frontotemporal dementia will show up differently on PET scans than Alzheimer disease, and amyloid imaging will be much clearer-cut in Alzheimer disease than in FTD.

TCPR: What kind of story would you hear from a patient's family member that would make you think there's a good chance the patient has frontotemporal dementia?

Dr. Kaufman: I might hear family members talk about the development of behavioral disturbances, such as manic or depressive symptoms, rather than simply memory impairment or poor judgment. In some patients with frontotemporal dementia, language impairment will be the primary symptom.

TCPR: Why is it important to distinguish between frontotemporal dementia and Alzheimer's?

Dr. Kaufman: It is more important to distinguish frontotemporal dementia from psychiatric disturbances—bipolar disorder, primary depression, or personality disorder. So, the difference is not so much between frontotemporal dementia and Alzheimer disease as it is between frontotemporal dementia and midlife psychiatric illnesses. Because there is more of a familial tendency among frontotemporal dementia patients than there is among Alzheimer disease patients, it is good for the family to have information on this distinction.

TCPR: What are some of the treatment implications or differentials between the two conditions?

Dr. Kaufman: If the clinical diagnosis is clearly frontotemporal dementia and confirmatory tests, such as fluorodeoxyglucose (FDG)-positron emission tomography (PET), are unnecessary, therapy should be directed first toward disruptive behavior. Caregivers might make changes in the physical and psychologic environment, such as stopping driving and potential social confrontations. When language impairment is a major symptom, speech therapy may be helpful in preserving patients' ability to communicate. Depending on the symptoms, some neurologists prescribe SSRIs or SNRIs (Rabinovici GD and Miller BL, *CNS Drugs* 2010;24(5):375–398). Antipsychotic agents' risks may preclude their use in all but extreme cases of disruptive behavior. Unlike in treatment of Alzheimer disease, cholinesterase inhibitors and memantine may worsen symptoms in frontotemporal dementia (Kirshner HS, *Neuropsychiatr Dis Treat* 2014;10:1045–1055). Treatment of Alzheimer disease symptoms also initially rests on general support, adjusting cognitive expectations, and managing symptoms. Symptomatic treatment of depression and disruptive behaviors do not occur with such regularity, but the treatments would be similar. Here, cholinesterase inhibitors and memantine slow the progression of cognitive impairments. Unfortunately, no treatments reverse the pathology of either frontotemporal dementia or Alzheimer disease—but promising studies are underway.

TCPR: Thank you for your time, Dr. Kaufman.

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Q&A With the Expert

The Neuroscience Behind Addictions and SSRIs

Edmund M. Higgins, MD

Clinical associate professor, Psychiatry and Behavioral Sciences, Medical University of South Carolina. Co-author of The Neuroscience of Clinical Psychiatry: The Pathophysiology of Behavior and Mental Illness, *3rd ed. (Wolters Kluwer).*

Dr. Higgins has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

TCPR: One of the reasons we wanted to interview you was to get insight into how we can talk to patients about the neuroscience behind their disorders. A lot of us know some of the science, but why is it good for us to learn more?

Dr. Higgins: I think it's important because having patients understand the neuroscience not only better educates them, but also can help them understand why it's important to stay on their treatments.

TCPR: Let's begin by talking about educating patients in terms of what's really going on in their brain when they have a heroin use disorder. How can we help patients understand that process, which can then help them with recovery?

Dr. Higgins: Well, I'd start by saying to the patient, "All the opioids (heroin, morphine, oxycodone, fentanyl, etc) function in the brain because they simulate naturally occurring brain molecules (eg, endorphins). Typically, we only get a little squirt of endorphins when we get a reward like earning a good grade, winning a race, or being kissed. The opioids hijack this naturally occurring reward system, and people can feel GREAT without having to exert any effort. However, the brain, in all its wisdom, recognizes this is a problem and recalibrates the system by reducing the number of receptors on the neurons. Consequently, it takes more endorphins (or heroin) to get the same good feeling."

TCPR: That sounds like a straightforward approach, but how do you then further explain to the patient on heroin what you mean by receptors, and how they function?

Dr. Higgins: If we think of the molecules (the endorphins or the opioids) as "keys" and the receptors on the neurons as "locks," then one needs the right key in the lock to get the reward—to turn on the good feelings. The brain likes to keep things in equilibrium—like keeping body temperature at 98.6 degrees. So, to not overwhelm the reward system, the brain starts reducing the number of locks. It does this by turning off the DNA that makes the receptors. Consequently, one needs more of the keys (molecules) to open the ever-decreasing locks (receptors); for someone with a substance use disorder, this impairs the experience of normal life. Because there are fewer locks to open in response to life's simpler, more subtle pleasures, life becomes gray (when not on drugs).

TCPR: As clinicians, how can we better understand this process?

Dr. Higgins: Instead of allowing the naturally occurring neurotransmitter chemicals to do their job, heroin binds to and activates specific mu-opioid receptors in the brain, causing an unnatural release of the neurotransmitter dopamine (see: https://www.drugabuse.gov/publications/research-reports/heroin/how-heroin-used). Heroin does this while causing a reduction in the number of brain receptors, which the neurons need to properly function (Chorbov WM et al, *J Opioid Manag* 2011;7(4):258–264). I tell the patient, "Once you stop the heroin, you will go through withdrawal, but if you then stay clean and sober, those receptors will rejuvenate and get your brain back to a more normal level."

TCPR: So, you're saying that, if a patient is abstinent for a while, the receptor factory will get revved up again?

Dr. Higgins: Exactly. I tell the patient, "Your genes will get turned back on and they'll start manufacturing more receptors (or "locks," if you're following my earlier metaphor). In due time, you won't feel as horrible as you feel now." However, trying to find joy in normal life can be a struggle for someone with substance dependence. This is the curse of heroin. But I think we need to tell patients that, if they can stay clean and sober long enough, other avenues are going to open up; that they'll become involved in more positive and healthier activities, including jobs and relationships. But the first step is getting through this withdrawal and then staying clean and sober. This may be why the faith-based programs are more effective than "just say no." A spiritual belief gives the abuser something to hang on to while the brain resets.

TCPR: Another topic we often find ourselves discussing with patients is selective serotonin reuptake inhibitors (SSRIs). Although these are probably the most common medications we discuss when it comes to depression, we don't know a lot about how SSRIs work. From a neuroscience standpoint, what should we know here?

Dr. Higgins: The most interesting aspect of the neuroscience of antidepressants is the growth factor proteins, such as brain-derived neurotropic factor (BDNF). For whatever reason, depression seems to reduce BDNF, which in turn causes a shrinking of the neurons. SSRIs, like any effective treatment for depression, can stimulate the DNA to produce more BDNF (Lee BH and Kim YK, *Psychiatry Investig* 2010;7(4):231–235). We've seen in studies with rats and postmortem research with humans that BDNF is increased with SSRIs, serotonin and norepinephrine reuptake inhibitors (SNRIs), as well as lithium, transcranial magnetic stimulation, and electroconvulsive therapy. We imagine psychotherapy does it as well, but we just don't know—nobody can get a rat model for psychotherapy, and we obviously can't conduct this sort of testing on the brains of living people.

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Research Updates IN PSYCHIATRY

ADHD

Dose Maintenance, Reduction With Antipsychotics

REVIEW OF: Zhou Y et al, *Journal of Psychopharmacology* 2018. doi:10.1177/0269881118756062

Once patients with schizophrenia are stabilized on an antipsychotic in the acute phase of their treatment, guidelines are unclear on how to continue dosing. Some guidelines recommend lowering the dose, others recommend maintaining the dose, and others give no firm recommendations whatsoever.

For fear of relapse, many clinicians never lower the dose, so many patients are simply kept on the higher acute-phase doses. These doses can be associated with more side effects, including extrapyramidal symptoms, metabolic syndrome, and impaired cognitive function.

This 52-week, single-blinded (rater-blinded), randomized controlled study sought data on maintenance and reduction using 2 frequently prescribed antipsychotics. Relapse was defined as a score of ≥ 4 on the Positive and Negative Syndrome Scale (PANSS) on at least one of the following: delusion, conceptual disorganization, hallucinatory behavior, or suspiciousness.

Researchers studied 75 stabilized schizophrenic patients, who were prescribed either risperidone (≥ 4 mg/day) or olanzapine (≥ 10 mg/day). They were randomly divided into a maintenance group (n = 38) and a dose-reduction group (n = 37).

In the maintenance group, the dose of medication remained unchanged. In the dose-reduction group, the dose of antipsychotic was reduced by 25% for the first 4 weeks, then reduced by 50% of the original dose for the remaining 48 weeks. Doses were never lowered below minimum recommendations—ie, below 2 mg/day for risperidone or below 5 mg/day for olanzapine.

Over 52 weeks, relapse rates were not significantly different between the groups, with relapse of only 4 patients in the dose-reduction group and 6 patients in the maintenance group.

A 50% dose reduction of antipsychotics did not lead to any worsening of psychotic symptoms. In fact, patients on the lower doses had fewer extrapyramidal symptoms ($p = 0.012$), lower body mass index ($p = 0.005$), improved cognitive function ($p = 0.001$), and improved negative symptoms overall ($p < 0.001$).

TCPR'S TAKE

Despite a small sample size, using single rather than double blinding, and being limited to only 2 antipsychotics, this study offers much-needed evidence to guide some important clinical decisions. During the maintenance phase with our stabilized schizophrenic patients, careful antipsychotic dose reduction (by 25% over the first 4 weeks, and then by 50% thereafter) is worth trying.

—Adam Strassberg, MD. Dr. Strassberg has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

ANTIDEPRESSANTS

Lithium Favored in Treatment Effectiveness Study

REVIEW OF: Lahteenvuo M et al, *JAMA Psychiatry* 2018;75(4):347–355

A new study from Finland shows that lithium may be more effective than other treatments in reducing the risk of psychiatric rehospitalization in patients with bipolar disorder.

Using a nationwide Finnish database, the authors examined the risk of rehospitalization for 18,000 patients with bipolar disorder—including psychiatric, cardiovascular, and all-cause hospitalization—from January 1, 1987 to December 31, 2012, then determined the risk of a rehospitalization based on the patients' use of various medications.

Over the study period, 9,721 of the patients (54%) suffered at least 1 psychiatric rehospitalization. Patients on lithium had the lowest risk for all-cause rehospitalization (hazard ratio [HR] 0.71 [95% CI, 0.66–0.76]), and for psychiatric rehospitalization (HR 0.67 [95% CI, 0.6–0.73]).

In addition to the findings on lithium, researchers also revealed the following about other psychotropic treatments:

- Long-acting injectable formulations of antipsychotic medications were more effective than their oral antipsychotic counterparts at reducing the risk of rehospitalization.
- Quetiapine fumarate, the most frequently used antipsychotic treatment in the population, was only modestly effective at reducing the risk of psychiatric rehospitalization.
- Benzodiazepines were linked to an increased risk for both psychiatric and all-cause rehospitalization.

TCPR'S TAKE

Although most of our treatment guidelines are based on randomized controlled trials, observational studies have many important findings to contribute to evidence-based medicine, and they are an alternative means to gauge effectiveness of various treatments.

The study findings correlate well with our clinical and anecdotal experience. Lithium is highly effective for bipolar disorder and should be a first-line treatment; it is also particularly effective for maintenance therapy. Long-acting antipsychotics may be more effective than their corresponding oral agents in preventing rehospitalizations, and we should consider their use whenever feasible. Long-term benzodiazepine use remains risky and problematic.

—Adam Strassberg, MD. Dr. Strassberg has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

Clarification From the April 2018 Issue

The research update published in the April 2018 issue of *TCPR*, entitled "Lisdexamfetamine for BED: How Effective Over the Long Term?" was ascribed to Robert T. Rubin, MD, PhD. In reality, the article was an extensive rewrite of an original draft submitted by Dr. Rubin, and the author was mistakenly not shown the final version for approval. Dr. Rubin has indicated that the rewrite does not reflect his perspectives as originally submitted. Our apologies to Dr. Rubin for not showing him the final version before publication.

CME Post-Test

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For those seeking ABPN Self-Assessment (MOC) credit, a pre- and post-test must be taken online at http://thecarlatcmeinstitute.com/self-assessment/

Below are the questions for this month's CME/CE post-test. This page is intended as a study guide. Please complete the test online at www.TheCarlatReport.com. Note: Learning Objectives are listed on page 1.

1. According to a recent study, which of the following medications was noted to have a higher response rate as well as a lower dropout rate than other antidepressants? (LO #1)

   [ ] a. Reboxetine [ ] b. Fluvoxamine [ ] c. Mirtazapine [ ] d. Doxepin

2. Your 55-year-old patient presents with a tremor when he sticks out both hands for 15 seconds, but not when they are at rest in his lap during the remainder of your appointment. These are tremor symptoms commonly associated with Parkinson disease. (LO #2)

   [ ] a. True [ ] b. False

3. According to a recent study, stabilized schizophrenic patients receiving a reduced dose of either risperidone or olanzapine over a course of one year had which of the following outcomes in comparison to the maintenance group? (LO #3)

   [ ] a. No significant differences in either psychotic symptoms or relapse rates after 1 year
   [ ] b. Increase in psychotic symptoms but no significant difference in relapse rates after 1 year
   [ ] c. No significant change in psychotic symptoms but higher relapse rates after 1 year
   [ ] d. Significant worsening of psychotic symptoms and higher relapse rates after 1 year

4. One significant result of the recent meta-analysis on antidepressants is the evidence supporting the beneficial long-term use of antidepressants. (LO #1)

   [ ] a. True [ ] b. False

5. Which of the following statements about the relationship between brain-derived neurotropic factor (BDNF) and depression is true? (LO #2)

   [ ] a. Depression seems to increase BDNF, which in turn causes a shrinking of the neurons
   [ ] b. Depression seems to reduce BDNF, which in turn causes a shrinking of the neurons
   [ ] c. Depression seems to increase BDNF, which in turn causes a growth of the neurons
   [ ] d. Depression seems to reduce BDNF, which in turn causes a growth of the neurons

Expert Interview—The Neuroscience Behind Addictions and SSRIs

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TCPR: Let's imagine a patient says to you, "You're saying that my depression is due to my neurons shrinking? What does that mean, doc? Will the medication I'm taking (the SSRI) help get me well?" What would you tell the patient?

Dr. Higgins: I would tell that patient, "Yes, since neurons control brain function, the reason for your depression appears to be a small shrinkage of some neurons." It's not dementia, or a neuronal loss; more like a thinning of the neuron branches. The SSRI will increase the growth factor proteins or BDNFs. A good way to put this in simple terms for the patient might be to say that sertraline (Zoloft), or any other antidepressant, can be like brain fertilizer—like throwing fertilizer on a lawn that's gotten a little thin and brown. SSRIs, of course, are not exactly like fertilizer, but they do stimulate your neurons to grow and branch out.

TCPR: I thought SSRIs increase serotonin and possibly help restore the chemistry in the brain. Is that inaccurate? Do SSRIs work some other way?

Dr. Higgins: Well, that was a very popular idea, and it's really a simple way to explain treatment. Sertraline, for example, does block the serotonin reuptake inhibitor. The idea has been that maybe there's not enough serotonin when a person is depressed and more when the person is treated, but research has failed to prove this true. What you can show is that antidepressants start a cascade of events in the cell that ultimately leads to the DNA and gene expression. So, it looks like the antidepressants are turning on something, such as BDNF, which explains why it takes weeks for antidepressants to be effective. They don't simply replace serotonin in the sense of putting oil in your car. It takes some time for antidepressants to sink in, and that's

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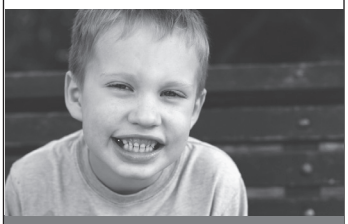

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Depression

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probably the process of getting down to the DNA and stimulating the growth factor proteins, which then stimulates nerve growth.

TCPR: We've been through a lot of theories about how antidepressants work, but is what you laid out here something that neuroscientists now hypothesize as a major part of the actual story?

Dr. Higgins: I would say, as a general opinion, that there are many smart people who believe this kind of model. I've learned from them. I'm not out there doing the research; I'm just reading what they are writing. But not everybody accepts this. Depression is very confusing, and there is no general consensus in terms of what's going on or even what's wrong with the brain. For example, if you were going to biopsy the brain of a depressed person, where would you do it? Nobody really knows. It's really hard to identify where the specific problem lies. So, a lot of this is speculation. The other complication is that we call it depression, but "depressions" might be more accurate—it's probably a number of different kinds of illnesses. Mark George, MD, my colleague and co-author, likes to point out that a hundred years ago we used to simply call a cough a cough, but now we might call it tuberculosis or influenza. We believe that in the future we'll have different names for different types of depression as we continue to learn more about the types of mechanisms that cause it.

TCPR: Thank you for your time, Dr. Higgins.

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